Overcoming Trastuzumab Resistance in Breast Cancer
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ABSTRACT
A targeted therapy using the antibodies Trastuzumab (Genentech, CA) developed to block HER2 signaling has been successfully used to treat patients with metastatic breast cancers that overexpress HER2. However, resistance to trastuzumab therapy is a major obstacle in the clinical management of HER2+ breast cancer. Studies have suggested an interesting association between the mechanism of resistance to trastuzumab and cyclin-dependent kinase inhibitor p27, a potent inhibitor of cell division. Decreased protein levels of p27 correlate with poor prognoses in patients with breast cancer and other tumor types. Recently, it has been discovered that c-Jun activation domain binding protein (JAB1), a negative regulator of p27, mediates p27 nuclear-to-cytoplasmic export and degradation by the ubiquitin-proteasome pathway. Thus, JAB1 contributes to the loss of p27 that is seen in over 50% of breast cancer tumors and is related to poor clinical outcomes. JAB1 plays an important role in the pathogenesis of breast cancer and represents an ideal target for therapeutic intervention, especially against trastuzumab resistance in HER2-overexpressing breast cancer cells. However, no therapies have been developed to target JAB1, even though disruption of its oncogenic activity would likely be a highly effective and safe treatment option for patients with advanced breast cancer. Based on our preliminary data, we hypothesize that overexpression of JAB1 plays a crucial role in the mechanism of resistance to trastuzumab through negative regulation of the cell cycle inhibitor p27. However, new strategies need to be developed to block JAB1’s oncogenic function, because silencing JAB1 approach cannot be applied to human therapy. We propose that the most appropriate strategy to control JAB1 activity will be to develop an inhibitor that antagonize the interaction between JAB1 and p27. This innovative approach of using JAB1 to reestablish cell-cycle arrest in tumor cells and the high-risk identification of potential small-molecule inhibitors could be a powerful new therapeutic tool for breast cancer patients. Drug discovery for early or late stage breast cancer would be invaluable for patients. The studies proposed in this pilot application would provide the preliminary data necessary for which additional funding can be applied to further develop approaches to elucidate the mechanism of breast tumorigenesis and resistance to trastuzumab.